
STAT3 Phosphorylation at Tyrosine 705 and Serine 727 Differentially Regulates Mouse ESC Fates.

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Authors: Guanyi Huang, Hexin Yan, Shoudong Ye, Chang Tong, Qi-Long Ying

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Public Summary:

Embryonic stem cells (ESCs) can be maintained in culture indefinitely while retaining the ability to make any type of cell in the body, therefore offering a potentially important renewable source for applications in cell replacement therapies. ESCs also provide a powerful tool for addressing some fundamental questions in basic biology. How ESCs retain the ability to produce more of themselves (self-renewal), however, remains largely unknown. STAT3 is a protein that plays an important role in controlling ESC fate. STAT3's activity in the cell is largely controlled by its two phosphorylation sites: tyrosine 705 and serine 727. In this study, we found that STAT3 phosphorylations at tyrosine 705 and serine 727 play distinct roles in controlling ESC fate. While phosphorylation at tyrosine 705 is essential for mouse ESC self-renewal mediated by STAT3, phosphorylation at serine 727 is dispensable, serving only to promote ESC proliferation. We also found that phosphorylation of STAT3 at serine 727 is important for efficient neural differentiation of ESCs. Our findings will help us to better control ESC fate, a step that is critical if the full potential of ESCs in both research and clinical application is to be realized.

Scientific Abstract:

STAT3 can be transcriptionally activated by phosphorylation of its tyrosine 705 or serine 727 residue. In mouse embryonic stem cells (mESCs), leukemia inhibitory factor (LIF) signaling maintains pluripotency by inducing JAK-mediated phosphorylation of STAT3 Y705 (pY705). However, the function of phosphorylated S727 (pS727) in mESCs remains unclear. In this study, we examined the roles of STAT3 pY705 and pS727 in regulating mESC identities, using a small molecule-based system to post-translationally modulate the quantity of transgenic STAT3 in STAT3(-/-) mESCs. We demonstrated that pY705 is absolutely required for STAT3-mediated mESC self-renewal, while pS727 is dispensable, serving only to promote proliferation and optimal pluripotency. S727 phosphorylation is regulated directly by fibroblast growth factor/Erk signaling and crucial in the transition of mESCs from pluripotency to neuronal commitment. Loss of S727 phosphorylation resulted in significantly reduced neuronal differentiation potential, which could be recovered by a S727 phosphorylation mimic. Moreover, loss of pS727 sufficed LIF to reprogram epiblast stem cells to naive pluripotency, suggesting a dynamic equilibrium of STAT3 pY705 and pS727 in the control of mESC fate. *Stem Cells* 2014;32:1149-1160.

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